REMARKS

I. Status of the Claims

Claims 29-60 are pending in the application. Claims 52-57, 59 and 60 are withdrawn pursuant to a restriction requirement. Claims 29-51 and 58 have been examined and stand rejected, variously, under 35 U.S.C. §112, first paragraph and 35 U.S.C. §112, second paragraph. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

II. Substitute Sequence Listing

Applicants hereby submit a substitute sequence listing with SEQ ID NOS:1-29. SEQ ID NOS:1-5 are newly included, and reflect SEQ ID NOS:1-5 from the priority PCT application filed along with applicants' translated specification, and also incorporated by reference therein. An accompanying amendment corrects the numbering of SEQ identifiers in the specification as previously inserted by the second preliminary amendment filed on January 12, 2004.

III. Objection to the Claims

Claim 58 is objected to for use of the term "eukaryotic cell" which is said to read on *in vivo* embodiments. Applicants have provided the suggested amendment which is believed to address the objection.

IV. Rejection Under 35 U.S.C. §112, First Paragraph

Claims 29-51 and 58 stand rejected under the first paragraph of §112 as lacking enablement. Applicants traverse the rejection and respond below based on the particular aspects of the rejection.

A. Scope of Eukaryotic Cells and Lambda Integrases

The examiner, in arguing that the scope of the claims is inappropriate, has commented that the claims are overly broad in reciting that the claimed invention may be employed in ***any*** eukaryotic cells, using ***any*** lambda integrase. Applicants respectfully traverse.

The present invention recites the use of lambda integrase Int. Thus, it is not clear what the examiner means by the use of "any" lambda integrase. To applicants' knowledge, there is only one integrase from bacteriophage lambda, namely, the Int integrase recited in the instant claims. Therefore, it is believed the rejection is improper and should be withdrawn.

Turning to the issue of eukaryotic cells, applicants submit that it is the examiner's burden to establish the applicants' presumptively enabling disclosure is ***not***, in fact, enabling. *In re Marzocchi*, 169 USPQ 370 (CCPA 1971). In fact, the examiner has provided no evidence to suggest that the source of the eukaryotic host cell makes any difference whatsoever in the operability of lambda Int. In fact, a central aspect of the invention is that applicants have identified the factors necessary to achieve integration/excision in eukaryotic cells. As such, applicants submit that the burden for establishing non-enablement has not been met, and the rejection is thus improper. Reconsideration and withdrawal of this rejection is also requested.

B. SEQ ID NOS:1-4

The examiner has indicated that the *Wands* factor dealing with the state and unpredictability of the art works to the detriment of the enablement of applicants' specification. In particular, the examiner notes that SEQ ID NOS:1-4 do not apparently reflect the sequences of *att*L, *att*R, *att*B and *att*P sequences, but instead, reflect 5' and 3' primers for cloning thereof.

As discussed above, the sequences for SEQ ID NOS:1-5 were inadvertantly omitted from the sequences listings previously filed in this case. The new sequence listing, provided herewith, includes the proper *att*L, *att*R, *att*B and *att*P sequences (SEQ ID NOS:1-4). Thus, it is believed that this correction addresses a significant portion of this aspect of the rejection.

Regarding the unpredictability allegedly stemming from the work of Lorbach *et al.*, applicants traverse the examiner's assertion that this paper somehow undercuts the enablement of the claimed invention. In essence, Lorbach *et al.* report on the same data as presented in the instant application, albeit with less detail. Thus, the experiment that the examiner points to in Lorbach *et al.* is the same control experiment reported in Example 7 of the instant application discussed below. These data do not undercut enablement by showing any inoperability, but instead, constitute the proper control so that the positive data can be validated.

In sum, there is no reason to suspect that SEQ ID NOS:1-4, when provided with Int and the proper factors as described in the instant specification, cannot facilitate integration/excision. Therefore, reconsideration and withdrawal of the rejection is respectfully requested.

C. Activity/Inactivity of Integrases

Another relevant *Wands* factor is said to be the amount of guidance provided in the specification, or the alleged lack thereof. As discussed above, applicants submit that the examiner has misunderstood the nature of the present invention, and the data provided in support thereof. The wild-type Int factor requires the IHF cofactor in recombination reactions involving attB/attP, and in the case of attL/attR, both IHF and the cofactor Xis are required. In contrast, the mutant Int requires no cofactors of attB/attP reactions, and only Xis for attL/attR reactions.

This is reflected by page 13, lines 3-23, which states "In eukaryotic cells the mutants need only the co-factor Xis for the recombination between attL/attR."

Furthermore, on page 14, lines 1-17, it is stated that "Both wild-type and Int mutants can only catalyze the so-called integrative recombination without addition of further factors, *i.e.*, they recombine *att*B with *att*P and not *att*L with *att*R if stably integrated into the genome of the cells. The wild-type integrase needs for the so-called excision recombination the factors IHF, Xis and negative super coiling. The Int mutants Int-h and Int-h/218 need for the excision recombination only the Xis factor."

Finally, the example cited by the examiner (see page 7 of Office Action) was performed to demonstrate that neither Int, wild-type or mutant, was able to act on attL/attR sequences without the co-factor Xis.[1] This control does not contradict the present invention as claimed. Rather, the experiments provided in the instant specification demonstrate that the claimed methods are indeed operative. Thus, there is no proper challenge to the enablement of these claims based merely on the question of Int function.

In light of the foregoing, applicants respectfully request reconsideration and withdrawal of the rejection.

V. Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 49-51 stand rejected under the second paragraph of §112. Specifically, the claims stand rejected for the recitation of "steps (a)-(c)" in referring to claim 29, which only recites

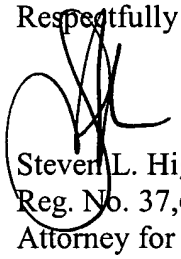
[1] The excision reaction, *i.e.*, using attR/attL, cannot be performed with Int or mutant Int alone. Therefore, a two step recombination is required: (i) the integrative recombination using attB/attP thereby generating attR/attL; and (ii) the controlled excision reaction when adding Xis. If the integrase was able to perform the excision reaction without adding Xis, a uncontrolled "flip-flop" mechanism would occur in step (ii).

steps (a) and (b). Claim 49 has been amended to refer to steps (a) and (b), and thus the rejection is believed to be overcome.

VI. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to the effect is earnestly solicited. Should the examiner have any questions regarding the content of this response, a telephone call to the undersigned is invited.

Respectfully submitted,



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